



4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2012-D-0071]

Draft Guidance for Industry: Modified Risk Tobacco Product Applications; Availability; Agency Information Collection Activities; Proposed Collection; Comment Request

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a draft guidance for industry entitled "Modified Risk Tobacco Product Applications." The draft guidance provides information about submitting applications for modified risk tobacco products under the Federal Food, Drug, and Cosmetic Act (the FD&C Act). The draft guidance describes the information that the FD&C Act requires you to submit in your modified risk tobacco product application and the scientific evidence FDA recommends you submit to support your application. The draft guidance also permits the filing of a single application for any modified risk tobacco product that is also a new tobacco product under the FD&C Act.

DATES: Although you can submit written or electronic comments on this guidance at any time (see 21 CFR 10.115(g)(5)), to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance, submit electronic or written comments on the draft guidance by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER]. Submit electronic or written comments on the proposed collection of information by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER].

ADDRESSES: Submit written requests for single copies of the draft guidance document entitled "Modified Risk Tobacco Product Applications" to the Center for Tobacco Products, Food and Drug Administration, 9200 Corporate Blvd., Rockville, MD 20850-3229. Send one self-addressed adhesive label to assist that office in processing your request or include a fax number to which the draft guidance may be sent. See the SUPPLEMENTARY INFORMATION section for electronic access to the draft guidance document.

Submit electronic comments on the draft guidance, including comments on the proposed collection of information, to <http://www.regulations.gov>. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Identify comments with the docket number found in brackets in the heading of this document.

FOR FURTHER INFORMATION CONTACT:

With regard to the draft guidance:

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With regard to the proposed collection of information:

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#### SUPPLEMENTARY INFORMATION:

##### I. Background

On June 22, 2009, the President signed the Family Smoking Prevention and Tobacco Control Act (Public Law 111-31) (Tobacco Control Act) into law. The Tobacco Control Act grants FDA authority to regulate the manufacture, marketing, and distribution of tobacco products to protect public health generally and to reduce tobacco use by minors. Congress found that it is essential that, prior to marketing tobacco products for use to reduce harm or the risk of tobacco-related disease or to reduce exposure to harmful substances associated with tobacco products, manufacturers be required to "demonstrate that such products...meet a series of rigorous criteria, and will benefit the health of the population as a whole" (section 2(36) of the Tobacco Control Act). Thus, section 101 of the Tobacco Control Act added section 911 (21 U.S.C. 387k) to the FD&C Act to prohibit the introduction or delivery for introduction into interstate commerce of any modified risk tobacco product unless an order issued by FDA pursuant to section 911(g) of the FD&C Act is effective with respect to such product. A modified risk tobacco product is any tobacco product that is sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products (section 911(b)(1) of the FD&C Act).

Section 911(l)(1) of the FD&C Act directs FDA to issue regulations or guidance (or any combination thereof) on the scientific evidence required for assessment and ongoing review of modified risk tobacco products. FDA is issuing this draft guidance in compliance with section 911(l)(1). When finalized, the draft guidance will provide industry with information on who submits modified risk tobacco product applications (MRTPAs), when to submit a MRTPA, what information section 911 of the FD&C Act requires applicants to submit in a MRTPA, what scientific evidence FDA recommends applicants include in a MRTPA, what information should be collected through postmarket surveillance and studies, how to organize and submit the MRTPA, and FDA's timeframe for review of a MRTPA. It will also provide for the filing of a single application for any modified risk tobacco product that is also a new tobacco product.

Section 911(l)(2) of the FD&C Act directs FDA to consult with the Institute of Medicine (IOM), and get the input of other appropriate scientific and medical experts, on the design and conduct of studies required for the assessment and ongoing review of modified risk tobacco products. FDA gave IOM its charge on February 2, 2011. IOM published its report on December 14, 2011. The report is available through <http://www.iom.edu/Reports/2011/Scientific-Standards-for-Studies-on-Modified-Risk-Tobacco-Products.aspx> and will be placed in the docket for this draft guidance. In order to get input from other experts, FDA held a public workshop on August 25 and 26, 2011, and established a docket, FDA-2011-N-0443, to receive public comments. FDA intends to consider the IOM report and comments submitted to the public workshop docket in preparing the final guidance.

## II. Significance of Guidance

FDA is issuing this draft guidance document consistent with FDA's good guidance practices regulation (21 CFR 10.115). The draft guidance, when finalized, will represent the

Agency's current thinking on "Modified Risk Tobacco Product Applications." It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute and regulations.

### III. Paperwork Reduction Act of 1995

Under the Paperwork Reduction Act of 1995 (the PRA) (44 U.S.C. 3501-3520), Federal Agencies must obtain approval from the Office of Management and Budget (OMB) for each collection of information they conduct or sponsor. "Collection of information" is defined in 44 U.S.C. 3502(3) and 5 CFR 1320.3(c) and includes Agency requests or requirements that members of the public submit reports, keep records, or provide information to a third party. Section 3506(c)(2)(A) of the PRA (44 U.S.C. 3506(c)(2)(A)) requires Federal Agencies to provide a 60-day notice in the Federal Register concerning each proposed collection of information before submitting the collection to OMB for approval. To comply with this requirement, FDA is publishing notice of the proposed collection of information set forth in this document.

With respect to the following collection of information, FDA invites comments on these topics: (1) Whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Draft Guidance for Industry: Modified Risk Tobacco Product Applications (OMB Control  
Number 0910-NEW)

This draft guidance describes the information that the FD&C Act requires you to submit in your MRTPA as well as FDA's recommendations regarding the scientific evidence that should be contained in a MRTPA for FDA to make an assessment and conduct an ongoing review of modified risk tobacco products. The draft guidance also permits the filing of a single application for any modified risk tobacco product that is also a new tobacco product under section 910 of the FD&C Act. The draft guidance document discusses, among other things: Who submits MRTPAs, when to submit a MRTPA, what information section 911 of the FD&C Act requires applicants to submit in a MRTPA, what scientific evidence FDA recommends applicants include in a MRTPA, what information should be collected through postmarket surveillance and studies, and how to organize and submit a MRTPA. The purpose of the proposed information collection is to allow FDA to collect statutorily mandated information regarding modified risk tobacco products and other information that will facilitate FDA's effective and efficient review of MRTPAs.

Modified risk tobacco products are tobacco products that are sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products (section 911(b)(1) of the FD&C Act). No person may introduce or deliver for introduction into interstate commerce any modified risk tobacco product unless an order issued pursuant to section 911(g) of the FD&C Act is effective with respect to that product (section 911(a) of the FD&C Act).

Under section 911(d) of the FD&C Act, a MRTPA must contain:

- A description of the proposed product and any proposed advertising and labeling;

- The conditions for using the product;
- The formulation of the product;
- Sample product labels and labeling;
- All documents (including underlying scientific information) relating to research findings conducted, supported, or possessed by the tobacco product manufacturer relating to the effect of the product on tobacco-related diseases and health-related conditions, including information both favorable and unfavorable to the ability of the product to reduce risk or exposure and relating to human health;
- Data and information on how consumers actually use the tobacco product; and
- Such other information as the Secretary may require.

Further, FDA's regulation implementing the National Environmental Policy Act of 1969 requires that "[a]ll applications or petitions requesting agency action require the submission of an [environmental assessment] or a claim of categorical exclusion" (21 CFR 25.15(a)).

Section 911(g) of the FD&C Act describes the demonstrations applicants must make to obtain an order from FDA. Sections 911(g)(1) and (2) of the FD&C Act set forth two bases for FDA to issue an order.

A "risk modification order" is an order permitting the introduction or delivery for introduction into interstate commerce of a tobacco product that FDA has found meets the criteria for an order under section 911(g)(1) of the FD&C Act. In order for FDA to issue a risk modification order under section 911(g)(1) of the FD&C Act, the applicant must demonstrate that the proposed modified risk tobacco product, as it is actually used by consumers, will:

- Significantly reduce harm and the risk of tobacco-related disease to individual tobacco users; and

- Benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products.

An "exposure modification order" is an order permitting the introduction or delivery for introduction into interstate commerce of a tobacco product that reduces or eliminates exposure to a substance and for which the available scientific evidence suggests that a measurable and substantial reduction in morbidity and mortality is likely to be demonstrated in future studies. In order for FDA to issue an exposure modification order, the applicant must satisfy all of the criteria for issuance of an order under section 911(g)(2) of the FD&C Act.

FDA may issue an exposure modification order under section 911(g)(2) of the FD&C Act (the "special rule") if it determines that the applicant has demonstrated that:

- Such an order would be appropriate to promote the public health;
- Any aspect of the label, labeling, and advertising for the product that would cause the product to be a modified risk tobacco product is limited to an explicit or implicit representation that the tobacco product or its smoke does not contain or is free of a substance or contains a reduced level of a substance, or presents a reduced exposure to a substance in tobacco smoke;
- Scientific evidence is not available and, using the best available scientific methods, cannot be made available without conducting long-term epidemiological studies for an application to meet the standards for obtaining an order under section 911(g)(1); and
- The scientific evidence that is available without conducting long-term epidemiological studies demonstrates that a measurable and substantial reduction in



morbidity or mortality among individual tobacco users is reasonably likely in subsequent studies (section 911(g)(2)(A) of the FD&C Act).

Furthermore, for FDA to issue an exposure modification order, FDA must find that the applicant has demonstrated that:

- The magnitude of overall reductions in exposure to the substance or substances, which are the subject of the application is substantial, such substance or substances are harmful, and the product as actually used exposes consumers to the specified reduced level of the substance or substances;
- The product as actually used by consumers will not expose them to higher levels of other harmful substances compared to the similar types of tobacco products then on the market unless such increases are minimal and the reasonably likely overall impact of use of the product remains a substantial and measurable reduction in overall morbidity and mortality among individual tobacco users;
- Testing of actual consumer perception shows that, as the applicant proposes to label and market the product, consumers will not be misled into believing that the product is or has been demonstrated to be less harmful, or presents or has been demonstrated to present less of a risk of disease than one or more other commercially marketed tobacco products; and
- Issuance of the exposure modification order is expected to benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products (section 911(g)(2)(B) of the FD&C Act).

In evaluating the benefit to health of individuals and of the population as a whole under sections 911(g)(1) and (g)(2) of the FD&C Act, FDA must take into account:

- The relative health risks the modified risk tobacco product presents to individuals;
- The increased or decreased likelihood that existing tobacco product users who would otherwise stop using such products will switch to using the modified risk tobacco product;
- The increased or decreased likelihood that persons who do not use tobacco products will start using the modified risk tobacco product;
- The risks and benefits to persons from the use of the modified risk tobacco product compared to the use of smoking cessation drug or device products approved by FDA to treat nicotine dependence; and
- Comments, data, and information submitted to FDA by interested persons (section 911(g)(4) of the FD&C Act).

Furthermore, FDA must ensure that the advertising and labeling of the MRTP enable the public to comprehend the information concerning modified risk and to understand the relative significance of such information in the context of total health and in relation to all of the tobacco-related diseases and health conditions (section 911(h)(1) of the FD&C Act).

FDA intends to determine whether it will issue an order under section 911(g) within 360 days after the receipt of a complete application and will issue such an order only if the application satisfies all the applicable requirements in section 911.

A risk modification order issued under section 911(g)(1) will be effective for the period of time specified in the order issued by FDA (section 911(h)(4) of the FD&C Act). An applicant to whom a risk modification order is issued under section 911(g)(1) must conduct postmarket surveillance and studies (section 911(i)(1) of the FD&C Act).

An exposure modification order issued under section 911(g)(2) will be effective for a term of not more than 5 years. FDA may renew an exposure modification order if the applicant files a new application, and FDA finds that the requirements for such order under section 911(g)(2) continue to be satisfied (section 911(g)(2)(C)(i) of the FD&C Act). Further, an exposure modification order will be conditioned on the applicant's agreement to conduct postmarket surveillance and studies and to submit the results of such surveillance and studies to FDA annually (section 911(g)(2)(C)(ii) and (iii) of the FD&C Act).

The postmarket surveillance and studies that all applicants who receive orders are required to conduct are intended to determine the effect of issuance of an order on consumer perception, behavior, and health, and enable FDA to review the accuracy of the determinations upon which an order was based (section 911(g)(2)(C)(ii) and (i)(1) of the FD&C Act). An applicant who receives a risk modification order must also conduct postmarket surveillance and studies that provide information FDA determines is otherwise necessary regarding the use or health risks involving the tobacco product (section 911(i)(1) of the FD&C Act).

If the proposed modified risk tobacco product is a new tobacco product within the meaning of section 910(a)(1), the new tobacco product must satisfy any applicable premarket review requirements under section 910 of the FD&C Act, in addition to any requirements under section 911 of the FD&C Act. A new tobacco product must be found to be substantially equivalent, exempt from the requirement to obtain a substantial equivalence determination, or have a marketing authorization order under section 910(c)(1)(A)(i). The collections of information relating to premarket review described in the "Guidance for Industry: Section 905(j) Reports: Demonstrating Substantial Evidence for Tobacco Products" (OMB control number 0910-0673), 21 CFR part 1107 (Establishment Registration, Product Listing, and Substantial

Equivalence Reports) (OMB control number 0910-0684), and "Draft Guidance for Industry: Applications for Premarket Review of New Tobacco Products" (OMB control number 0910-NEW) have been previously approved, or are pending approval, by OMB. An applicant may file the appropriate report or application to satisfy any applicable premarket review requirements and a separate application under section 911. In the alternative, the applicant may file a single application. The single application must include the information required for the applicable premarket review (i.e., substantial equivalence report, request of exemption from substantial equivalence requirements, or the information required for premarket review under section 910(b) of the FD&C Act), as well as the information required to support issuance of an order under section 911(g) of the FD&C Act. To the extent data or information contained in the premarket review portion of the application is also relevant to or required for the modified risk determination, the applicant may cross-reference that data or information rather than duplicate it in the modified risk portion of the application.

Description of respondents: The respondents to this collection of information are applicants who are responsible for creating and submitting modified risk tobacco product applications and who wish to obtain an FDA order to allow them to market their product. While it is expected that many of the respondents will be manufacturers, respondents could include importers, distributors, and retailers of tobacco products.

FDA estimates the burden of this collection of information as follows:

Table 1.--Estimated Annual Reporting Burden <sup>1</sup>					
Information Collected (Section(s))	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response (in hours)	Total Annual Hours
MRTPA (911(d) of FD&C Act)	3	1	3	45,200	135,600
Environmental	3	1	3	10	30

analysis (21 CFR 25.15)					
Request for a meeting prior to submitting a MRTPA	8	1	8	8	64
Submission of postmarket surveillance and study protocols (911(g)(2)(C)(ii) and 911(i)(2))	3	1	3	30	90
Conduct of postmarket surveillance and studies (911(g)(2)(C)(ii) and 911(i)(1))	5	1	5	40,200	201,000
Annual submission of results of postmarket surveillance and studies (911(g)(2)(C)(iii) and 911(i)(1))	5	1	5	140	700
Requests for renewal (911(g)(2)(C)(i) and 911(h)(4))	1	1	1	140	140
Total Reporting Burden Hours					337,624

<sup>1</sup> There are no capital costs or operating and maintenance costs associated with this collection of information.

Table 1 describes the annual reporting burden as a result of submitting a MRTPA. FDA estimates that it will receive 3 MRTPAs annually and that it will take the applicant 200 hours to collect the information necessary to submit a MRTPA under section 911 of the FD&C Act. FDA estimates it will take the applicant an additional 45,000 hours to conduct studies needed to support its MRTPA. FDA is also including an estimation of the burden associated with preparing environmental analyses. FDA estimates that it will take an additional 10 hours to prepare any environmental analyses. FDA encourages persons considering developing a MRTPA to meet with CTP to discuss MRTPA submission and investigational requirements. FDA anticipates that eight persons considering developing MRTPAs may request meetings with

FDA. FDA estimates it will take 8 hours to prepare a meeting request, including background information.

Section 911 of the FD&C Act requires applicants to whom FDA issues orders to conduct postmarket surveillance and studies and submit relevant information to FDA on an annual basis. Applicants must submit and receive FDA approval of surveillance protocols. FDA estimates that it will take 30 hours to collect and submit the protocol information to FDA. FDA estimates it will take the applicant an additional 40,200 hours to conduct the postmarket surveillance and studies. FDA estimates 5 applicants will submit results of postmarket surveillance and studies annually and it will take 140 hours to prepare each submission.

Because orders issued under section 911(g) are valid for only a set number of years, FDA expects applicants will submit requests for renewal. Because the dates on which orders are issued and the length of the period for which the order is valid will vary, FDA expects one request for renewal annually. FDA estimates that it will take 140 hours to prepare the request for renewal.

The total number of hours for this collection of information is estimated to be 337,624  $((3 \times (45,200+10)) + (8 \times 8) + (3 \times 30) + (5 \times 40,200) + (5 \times 140) + (1 \times 140))$ . These burden estimates were computed using FDA staff expertise and by reviewing comments received from recent FDA information collections for other tobacco-related initiatives.

#### IV. Request for Comments

FDA requests comments from interested parties on any of the topics addressed in the draft guidance. In addition, as stated in the "I. Background" section, FDA intends to consider the IOM report in preparing the final guidance. Therefore, FDA requests comments from interested

parties on the IOM report, which was issued on December 14, 2011. FDA specifically requests comments on:

- IOM's Recommendation 2: "The FDA should establish guidance that conveys an expected sequencing of studies, such that preclinical work is completed and submitted to the FDA before clinical (human subjects) work commences, and [FDA should establish] that there is a reasonable expectation based on preclinical work that a reduction or lack of harm will be seen in humans." Should FDA address expected sequencing of studies in its guidance? If the Agency should, what guidance should the Agency provide?; and
- IOM's Recommendation 10: "MRTP sponsors should consider use of independent third parties to undertake one or more key functions, including the design and conduct of research, the oversight of specific studies, and the distribution of sponsor funds for research. Such independent third parties should be approved by the FDA in advance of the research." Should FDA recommend such an approach in its guidance? If the Agency should, what guidance should the Agency provide?

Interested persons may submit to the Division of Dockets Management (see ADDRESSES) either electronic or written comments regarding this document. It is only necessary to send one set of comments. Identify comments with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

## V. Electronic Access

Persons with access to the Internet may obtain an electronic version of the draft guidance document at <http://www.regulations.gov> and

<http://www.fda.gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation/default.htm>.

Dated: March 28, 2012.

Leslie Kux,

Assistant Commissioner for Policy.

[FR Doc. 2012-7908 Filed 03/30/2012 at 11:15 am; Publication Date: 04/03/2012]